(3) H. D. Zook and J. A. Miller, *J. Org. Chem.*, **36**, 1112 (1971).
(4) R. Huisgen and W. Mack, *Chem. Ber.*, **93**, 332 (1960).
(5) R. Waack and M. A. Doran, *Chem. Ind. (London)*, 496 (1964).
(6) W. Glaze and R. West, *J. Am. Chem. Soc.*, **82**, 4437 (1960).
(7) P. D. Bartlett, C. V. Goebel, and W. P. Weber, *J. Am. Chem. Soc.*, **91**, 7425 (1969).
(8) Unpublished work of D. S. Stotz and W. L. Reilahan, The Pennsylvania State University.
(9) A. Kirrmann and J. Delpuech, *C. R. Acad. Sci.*, **257**, 127 (1963).

## Decarbalkoxylation of Isohexylmalonates

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*Received January 12, 1977*

A decade ago Krapcho reported that a geminal diester could be converted to the corresponding monoester by a novel one-step method.[1] The original procedure of sodium cyanide and dimethyl sulfoxide ($Me_2SO$) was subsequently extended to include other salts in wet $Me_2SO$ or wet dimethylformamide (DMF),[2] and it was further discovered that even the salt was unnecessary in the case of phenylmalonates.[3,4] While the pioneering work of Krapcho and co-workers served to define the structural range of diesters,[1-3] there has been no systematic study of the other reagents. In fact, a variety of conditions has been reported: sodium cyanide in $Me_2SO$,[5] lithium iodide and sodium cyanide in DMF,[6] and lithium chloride or sodium iodide[7a] or tetramethylammonium acetate[7b] in hexamethylphosphorictriamide. Recently, cyclic secondary or tertiary amines in hydrocarbon solvents have also been utilized for decarbalkoxylations.[8]

In connection with studies related to the synthesis of the gypsy moth sex pheromone, we required 1-bromo-6-methylheptane.[9,10] As an alternative to the published procedures, we have explored a route which involved the following reaction.

$$\underset{\mathbf{1}}{Me_2CH(CH_2)_3CH(CO_2R)_2} \rightarrow \underset{\mathbf{2}}{Me_2CH(CH_2)_4CO_2R}$$

**a**, R = Me; **b**, R = Et

The present work was undertaken to define the scope of this decarbalkoxylation step. Esters **1a** and **1b** were obtained by malonic ester syntheses. Hydrolysis, decarboxylation, and esterification gave authentic samples of **2a** and **2b** for calibration purposes. A standardized procedure for decarbalkoxylation was utilized to assess the effects of different salts, concentration, reaction times, and ester groups. The analytical procedure involved GLC determination of **1** and **2**; the isolated yield of crude product was 65–95%. The results are shown in Tables I and II. It is clear that an added salt is necessary; best results were obtained with 1 equiv. Previous work established that wet $Me_2SO$ was necessary.[3] In the present study, 2 equiv of water proved satisfactory. The more facile reaction of methyl esters compared to the corresponding ethyl esters was also observed by Krapcho, who has considered the mechanistic aspects.[11] Although the present study was not designed to elucidate reaction pathways, our results do establish that acid catalysis generated in situ is not operative.[12]

**Table I. Decarbalkoxylation of 1a by Various Salts in $Me_2SO$**

| Salt | Salt, mmol | Water, mmol | Reflux time, h | **2a**, %[a] |
|---|---|---|---|---|
| LiCl | 4 | 8 | 1 | >99 |
| | 4 | 8 | 0.5 | 99 |
| NaCl | 4 | 8 | 1 | 99 |
| | 4 | 4 | 1 | 99 |
| KCl | 4 | 8 | 1 | 98 |
| $CaCl_2 \cdot 2H_2O$ | 4 | 0 | 1 | >99 |
| | 4 | 0 | 0.5 | 99 |
| NaBr | 4 | 8 | 1 | 96 |
| $LiI \cdot H_2O$ | 4 | 0 | 1 | >99 |
| NaI | 4 | 8 | 1 | 97 |
| NaCN | 4 | 8 | 1 | >99 |
| | 4 | 8 | 0.5 | >99 |
| | 4 | 4 | 1 | >99 |
| | 4 | 0 | 1 | >99 |
| | 2 | 8 | 1 | 95 |
| $Na_2CO_3 \cdot H_2O$ | 4 | 0 | 1 | 96 |
| $Na_3PO_4 \cdot 12H_2O$ | 0.8 | 0 | 1 | 98 |
| None | | 8 | 1 | 10 |
| None | | 0 | 1 | 11 |

[a] Purity was determined by GLC and is based on **1a** and **2a**; no additional substances were detected. Values are the average (±1%) of duplicate runs.

**Table II. Decarbalkoxylation of 1b by Various Salts in $Me_2SO$**

| Salt | Salt, mmol | Water, mmol | Reflux time, h | **2b**, %[a] |
|---|---|---|---|---|
| LiCl | 4 | 8 | 2 | >99 |
| | 4 | 8 | 1 | 88 |
| NaCl | 4 | 8 | 2 | 99 |
| | 4 | 8 | 1 | 81 |
| KCl | 4 | 8 | 2 | >99 |
| | 4 | 8 | 1 | 83 |
| $CaCl_2 \cdot 2H_2O$ | 4 | 0 | 2 | 98 |
| | 4 | 0 | 1 | 91 |
| NaCN | 4 | 8 | 2 | >99 |
| | 4 | 8 | 1 | 99 |
| | 4 | 8 | 0.5 | 85 |
| | 4 | 4 | 1 | 95 |
| | 4 | 0 | 1 | 75 |
| | 2 | 8 | 1 | 93 |
| $Na_3PO_4 \cdot 12H_2O$ | 0.8 | 0 | 2 | >99 |
| | 0.8 | 0 | 1 | 90 |
| None | | 8 | 1 | 2 |
| | | 0 | 1 | 5 |

[a] Purity was determined by GLC and is based on **1b** and **2b**; no additional substances were detected. Values are the average (±1%) of duplicate runs.

### Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer and calibrated by a polystyrene film. Gas–liquid chromatography (GLC) was carried out on a Varian 1400 chromatograph with a 12 ft × 0.125 in. column of 10% Dow-Corning 710 on Chromosorb W, the helium flow rate was 30 mL/min, and the column was operated at 210 °C. Elemental analyses were obtained from the Analytical Services Laboratory, University of California, Berkeley.

**Materials.** Dimethyl sulfoxide ($Me_2SO$; Fisher Certified), 1-bromo-4-methylpentane (Chemical Samples Co.), and all salts (reagent grade) were used without further purification.

**Dialkyl Isohexylmalonates (1).** The reaction of 1-bromo-4-methylpentane with dimethyl sodiomalonate by the method of Adams and Kamm[13] gave 69% of **1a**: bp 85–87 °C (2 Torr); IR (neat) 1757 and 1736 $cm^{-1}$.

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.04; H, 9.11.

Similarly, the reaction with diethyl sodiomalonate gave 64% of **1b**: bp 142–144 °C (10 Torr); IR (neat) 1751 and 1733 $cm^{-1}$ [lit.[14] bp 136–139 °C (11 Torr)].

**Alkyl 6-Methylheptanoates (2).** Diester **1b** was converted by known procedures[15] to 6-methylheptanoic acid (**3**) in 95% yield, bp 85–88 °C (2 Torr); *p*-bromophenacyl ester, mp 67.5–67.6 °C [lit.[16] bp 128–129 °C (15 Torr); *p*-bromophenacyl ester, mp 67.7 °C]. Fischer esterification of **3** gave **2a**: bp 72.5–73.2 °C (11 Torr); IR (neat) 1745 $cm^{-1}$ [lit.[17,18] bp 73 °C (10 Torr); IR (neat) 1739 $cm^{-1}$]. Similarly, **3** gave **2b** in 59% yield: bp 52–53 °C (2 Torr); IR (neat) 1739 $cm^{-1}$ (lit.[19] bp 200.3 °C).

**General Reaction Procedure. A. Analytical Scale.** The following procedure was typical of that used for all experiments reported in Tables I and II.

To a 25-mL flask were added diester **1a** or **1b** (4.0 mmol), a salt (4.0 mmol), water (8.0 mmol), and $Me_2SO$ (10 mL). The heterogeneous reaction mixture was refluxed for 1 h, cooled, transferred to a separatory funnel containing 100 mL of water, and extracted with three 15-mL portions of hexane. The combined hexane extract was washed once with water, dried ($Na_2SO_4$), filtered, and concentrated at reduced pressure on a rotary evaporator.

The residual oil was analyzed by GLC. Authentic samples of **1a, 1b, 2a,** and **2b** were used to calibrate the detector response and determine the retention times (in min): **2a,** 1.8; **2b,** 2.2; **1a,** 4.6; and **1b,** 6.6. It was established by control runs that the detectable limit of diester in a mixture of 1 and **2** was 0.8%. No peaks other than **1** and **2** were observed in the product mixture.

**B. Preparative Scale.** A mixture of **1a** (4.4 g, 0.020 mol), sodium cyanide (1.0 g, 0.020 mol), water (0.72 mL, 0.040 mol), and $Me_2SO$ (50 mL) was refluxed for 1 h and worked up as above to give 2.3 g (72%) of **2a**: purity >99% by GLC.

**Acknowledgment.** The authors are indebted to Professor Krapcho for stimulating discussions and helpful suggestions.

**Registry No.**—**1a,** 62337-57-9; **1b,** 39953-95-2; **2a,** 2519-37-1; **2b,** 62337-58-0; **3,** 929-10-2; **3** *p*-bromophenacyl ester, 62337-59-1; 1-bromo-4-methylpentane, 626-88-0; dimethyl sodiomalonate, 18424-76-5; diethyl sodiomalonate, 996-82-7.

## References and Notes

(1) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967).
(2) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973).
(3) A. P. Krapcho, E. G. E. Jahngen, Jr., A. J. Lovey, and F. W. Short, *Tetrahedron Lett.*, 1091 (1974).
(4) C. L. Liotta and F. L. Cook, *Tetrahedron Lett.*, 1095 (1974).
(5) (a) W. S. Johnson, C. A. Harbert, and R. D. Stipanovic, *J. Am. Chem. Soc.*, **90,** 5279 (1968); (b) J. Harley-Mason and Atta-ur-Rahman, *Chem. Ind. (London),* 1845 (1968); (c) A. P. Krapcho and B. P. Mundy, *Tetrahedron,* **26,** 5437 (1970); (d) W. Kirmse, J. Knist, and J.-J. Ratajczak, *Chem. Ber.,* **109,** 2296 (1976).
(6) (a) B. M. Trost and T. J. Dietsche, *J. Am. Chem. Soc.,* **95,** 8200 (1973); (b) B. M. Trost and L. Weber, *J. Org. Chem.,* **40,** 3617 (1975).
(7) (a) M. Asaoka, K. Miyake, and H. Takei, *Chem. Lett.,* 1149 (1975); (b) W. S. Johnson, C. A. Harbert, B. E. Ratcliffe, and R. D. Stripanovic, *J. Am. Chem. Soc.,* **98,** 6188 (1976).
(8) (a) F. Texier, E. Marchand, and R. Carrie, *Tetrahedron,* **30,** 3185 (1974); (b) D. H. Miles and B.-S. Huang, *J. Org. Chem.,* **41,** 208 (1976).
(9) B. A. Bierl, M. Beroza, and C. W. Collier, *J. Econ. Entomol.,* **65,** 659 (1972).
(10) (a) H. J. Bestmann and O. Vostrowsky, *Tetrahedron Lett.,* 207 (1974); (b) H. J. Bestmann, O. Vostrowsky, and W. Stransky, *Chem. Ber.,* **109,** 3375 (1976).
(11) A. P. Krapcho, J. M. Eldridge, E. G. E. Jahngen, Jr., A. J. Lovey, W. P. Stephens, and J. F. Weimaster, Abstracts, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Sept 1976, No. ORGN-196.
(12) T. M. Santosusso and D. Swern, *J. Org. Chem.,* **41,** 2762 (1976).
(13) R. Adams and R. M. Kamm, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N.Y., 1941, p 250.
(14) H. Kondo and H. Suzuki, *Ber.,* **69,** 2459 (1936).
(15) E. B. Vliet, C. S. Marvel, and C. M. Hsueh, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 416.
(16) A. H. Milburn and E. V. Truter, *J. Chem. Soc.,* 3344 (1954).
(17) E. Rothstein and W. G. Schofield, *J. Chem. Soc.,* 4566 (1965).
(18) E. Wenkert, P. Bakuzis, R. J. Baumgarten, C. L. Leicht, and H. P. Schenk, *J. Am. Chem. Soc.,* **93,** 3208 (1971).
(19) P. A. Levene and C. H. Allen, *J. Biol. Chem.,* **27,** 433 (1916).

# Eremofortin C. A New Metabolite Obtained from *Penicillium roqueforti* Cultures and from Biotransformation of PR Toxin

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*Received January 17, 1977*

*Penicillium roqueforti* is a fungal species of particular interest because of the toxic compounds recently isolated from the mycelium of this species. These compounds include the indole alkaloids[1,2] and the sesquiterpenoid metabolites such as PR toxin (**3**) and related compounds.[3,4] We report here the isolation and characterization of a new sesquiterpenoid compound, eremofortin C (**4**). This compound was obtained using two methods: direct isolation from *P. roqueforti* culture media and biotransformation of PR toxin and eremofortin A[4] (**1**) by liver mixed-function oxidases.[5,6]

**Isolation and Characterization of Eremofortin C.** Eremofortin C was isolated from the culture media of a *P. roqueforti* strain by chloroform extraction. The chloroform extract was chromatographed on silica gel and crystallized from ethyl ether. The structure **4** was assigned on the bases of spectral data and various chemical reactions. The spectral characteristics of the compound indicated that it was closely related to PR toxin (**3**) and eremofortin A (**1**).

The IR spectrum (KBr) showed a hydroxyl group (3420, 3350 $cm^{-1}$), an $\alpha,\beta$-unsaturated ketone (1685 $cm^{-1}$), an isolated double bond (1650 $cm^{-1}$), and a conjugated double bond (1620 $cm^{-1}$). The mass spectrum of **4** showed a molecular ion at *m/e* 322. High-resolution mass spectral analysis indicated a molecular peak at *m/e* 322.14161 (calcd for $C_{17}H_{22}O_6$, 322.14163). The complex 250-MHz $^1H$ NMR spectrum appeared to be a superposition of the spectra of two acetylated compounds: $\delta$ $CH_3COO$ 2.18 and 2.19 ppm, two multiplets centered at $\delta$ 5.18 and 5.25 (H-3), and two singlets at $\delta$ 6.02 and 6.44 (H-9).

The equilibrium suggested by these data was proved by variable temperature $^1H$ NMR studies. Ratios of the areas of the H-9 peaks were measured at different temperatures. That at $\delta$ 6.02 ppm was attributed to compound **4a** and that at $\delta$ 6.44 ppm to compound **4b** after comparison with values obtained for H-9 in compounds **1, 3,** and **6**.[3,4] Results are given in Table I. An increasing temperature seemed to promote the formation of compound **4b** (79% at 95 °C). A lowering of these temperatures resulted in the recovery of the initial ratio of the two compounds.

The structure was confirmed by the following chemical reactions. Sodium borohydride reduction of PR toxin (**3**) yielded a crystalline substance. Chromatographic behavior and spectroscopic data (IR, $^1H$ NMR, mass spectrum) showed that this compound was identical with naturally occurring eremofortin C( **4a** $\rightleftarrows$ **4b**). Acetylation of eremofortin C yielded a unique compound **2** which crystallized from ethyl ether. The structure of **2** was assigned on the bases of spectral data by comparison with the previously mentioned metabolites.[4]

**In Vitro Metabolism of PR Toxin and Eremofortin A.** Four metabolites were obtained during incubation of PR toxin and eremofortin A with the microsomal enzymes of rat hepatocytes. Their chemical structures are shown in Scheme I.

All the metabolites obtained from 10 mg of compounds **1** or **3** were isolated from the enzymatic reaction medium by